

# Endothelial Dysfunction in Systemic Lupus Erythematosus

Simona Coman<sup>1</sup>, Mirela Parvu<sup>2</sup>, Lia Georgescu<sup>3</sup>

<sup>1</sup>Institute of Cardiovascular Disease – Clinic of Cardiology, Faculty of Medicine, UMPH Targu Mures

<sup>2</sup>University Emergency Hospital – Clinic of Rheumatology, Faculty of Medicine, UMPH Targu Mures

1. Carabă2008 (not cited)

2. Magadmi2004 (cited)

3. Ahmad2007 (cited)

**Background:** Systemic lupus erythematosus (SLE) patients have a significantly increased risk of coronary heart disease (CHD) that is not fully explained by classic risk factors. Endothelial dysfunction is an early stage in the process of atherogenesis. Our aim was to determine whether endothelial dysfunction occurs in SLE and whether it is associated with the occurrence of classic Framingham risk factors.

**Methods and Results:** We studied 54 women with SLE (1997 revised criteria) and 27 healthy women. Demographic and risk factor data were collected (cholesterol, triglycerides, smoking, diabetes mellitus, systolic and diastolic blood pressure). Endothelial function was assessed by flow-mediated dilation (FMD) in the brachial artery in response to reactive hyperemia. SLE activity was assessed using SLE Disease Activity Index (SLEDAI). Endothelial function was assessed by means of flow mediated dilation (FMD) on brachial artery, using B-mode ultrasonography. The statistical analysis was done using version 17.0 of the SPSS statistical package. The group of SLE patients was formed of 54 females, with the mean age of  $45,66 \pm 8,72$  years. The values of FMD were  $7,12 \pm 4,7$  % (SLE group) and  $21,32 \pm 3,12$  % (group control),  $p < 0.0001$ . The statistical analysis showed a strong inverse correlation between FMD and SLEDAI, a moderate inverse correlation between FMD and total cholesterol, systolic and diastolic blood pressure. After adjustment for other factors, SLE activity was associated with 1,27% lower FMD compared with control subjects.

**Conclusions:** Endothelial dysfunction is present in SLE patients even in the absence of traditional cardiovascular risk factors, due to disease activity. Patients with SLE have endothelial dysfunction that remained significant even after adjustment for other classic CHD risk factors. Understanding the mechanism(s) of endothelial dysfunction in SLE may suggest novel strategies for CHD prevention in this context.

**Keywords:** endothelial dysfunction, systemic lupus erythematosus (SLE), flow-mediated dilatation (FMD), coronary heart disease (CHD)

## Introduction

Systemic lupus erythematosus (SLE) represents the autoimmune disease, with a wide range of clinical and biological manifestations [1]. Despite the improvement of therapeutic regimes, the morbidity and mortality associated with SLE remained at high levels. In 1976, Urowitz et al. [2] postulated a bimodal mortality pattern in patients with this disease: in the first part of evolution, mortality is due to severe infections or to disease activity, but after 5 years of SLE course, mortality is caused by the accelerated atherosclerosis and its consequences. Premature coronary heart disease (CHD) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) and in younger women, the excess risk may be >50-fold [3]. SLE patients also have an increased prevalence of subclinical atherosclerotic disease detected using several modalities [4,5,6]. However, traditional risk factors alone do not explain the excess CHD risk and after adjusting for traditional risk factors, SLE itself remains independently associated with both clinical and subclinical outcomes [5, 6, 7].

In healthy subjects, endothelium is not a simple physical barrier between the blood flow and the underlying tissues. This structure has many functions, like: continuous regulation of vascular tone, leucocytes adhesion, maintenance of the balance between thrombotic and anticoagulant properties of the blood [8]. When these functions of the

endothelium are affected, endothelial dysfunction appears. Endothelial dysfunction is considered the first step in the atherogenetic process; it was identified even in patients with SLE, without cardiovascular risk factors [9]. Endothelial dysfunction in SLE is produced by the clustering of traditional risk factors such as smoking, diabetes mellitus, and hypercholesterolemia, adverse effects of treatment and SLE itself as an independent risk factor [1,10]. non-invasive method for the assessment of endothelial function is flow mediated vasodilation (FMD) on brachial artery, using vascular ultrasonography.

Therefore, our aims were to determine whether endothelial dysfunction occurred in women with SLE, whether it was explained by the presence of classic CHD risk factors, and whether SLE activity influence endothelial dysfunction.

## Material and methods

We performed a retrospective observational study in SLE subjects. The study was carried on two groups of subjects: SLE group, formed by 54 patients with SLE without renal involvement and group control, formed by 27 healthy sex and age-matched controls. The diagnosis of SLE was established based on American College of Rheumatology criteria.

Total cholesterol (Abbott photometry), triglycerides (Abbott reactive), were determined in all patients.

**Table I. Characteristics of the studied groups**

Parameters	LES group	Control group
Females	54	27
Mean age (years)	45,66 ± 8,72	45,88±8,14
Mean duration of SLE evolution (years)	9,37 ± 4,86	0
Total cholesterol (mg%)	223,20 ± 37,99	201,48 ± 46,75
HDL-colesterol (mg%)	44,92 ± 3,85	50,07 ± 1,56
Triglycerides (mg%)	176,51 ± 40,51	151,48 ± 35,93
Smoking (%)	23,43	77,32
SBP (mmHg)	150,16 ±17,39	139,07 ± 21,21
DBP (mmHg)	86,57 ± 7,25	81,85 ± 10,66
SLEDAI	10,64 ± 2,93	0

DBP – diastolic blood pressure, SBP – systolic blood pressure, SLEDAI – SLE Disease Activity Index

The SLE activity was assessed using SLE Disease Activity Index (SLEDAI).

Endothelial function was assessed by means of flow-mediated vasodilation on brachial artery, using B-mode ultrasonography (Philips HD7, with linear transducer of 7.5 MHz). Before the test, the patient was relaxed in a stable room temperature between 20–25 °C; the smoking was prohibited. The diameter of brachial artery was measured incident with the R wave of the electrocardiograph trace (D1). Then, ischemia was induced by inflating the pneumatic cuff to a pressure 50 mmHg above systolic one, in order to obliterate the brachial artery and induce ischemia. After 5 minutes, the cuff was deflated and the diameter was measured after 60 seconds post-deflation (D2). FMD was calculated with the formula:  $FMD = [(D2 - D1)/D1] \times 100$  [11].

We used version 17.0 of the SPSS statistical package. All the values were presented as mean ± standard deviation. For univariant dates analysis we used T test for independent variables (continuous variables with normal distribution on Kolmogorov-Smirnov test), Man-Whitney test (for continuous variables with non-normal distribution),  $\chi^2$  test (dihotomic variables). Multivariant analysis was used for multiple regression analysis. A significant level was set at  $p < 0.05$ .

**Results**

The demographic, clinical and biological characteristics of the studied groups are shown in Table I. In SLE group, FMD was lower than in the control group (Table II).

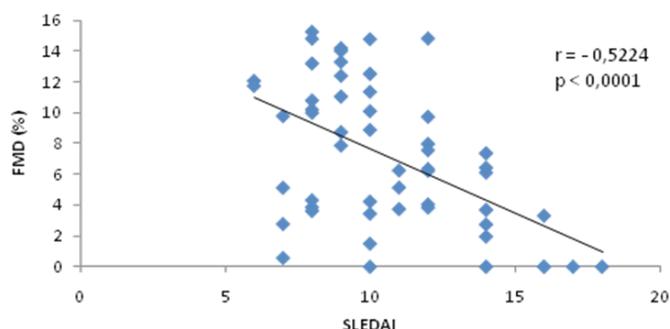


Fig. 1. Correlation between FMD and SLEDAI

**Table II. FMD in the studied groups**

	LES	Control	p
FMD (%)	7.12 ± 4.7	21.32 ± 3.12	<0.0001 extremely significant

**Table III. Correlations between FMD and SLE parameters**

Parameters	Correlation coefficient
SLEDAI	r = - 0.5224. p < 0.0001
Cholesterol	r = - 0.4405. p < 0.005
HDL-c	r = 0.6329. p < 0.0001
TG	r = - 0.5101. p < 0.0001
SBP	r = - 0.3158. p < 0.05 significant
DBP	r = 0.1532. p = 0.2687 not significant
DM	r = - 0.5007. p < 0.0001

DM – diabetes mellitus

The correlations between FMD and biological and immunological parameters are shown in Table III.

The statistical analysis showed: a strong inverse correlation between FMD and SLEDAI, a moderate inverse correlation between FMD and total cholesterol, systolic blood pressure, diabetes mellitus, a significant correlation between FMD and HDL-colesterol (Figures 1 and 2).

Multiple regression model shows that period of disease ( $p=0,009$ ), HDL-c ( $p=0,034$ ) and SLEDAI ( $p=0,0001$ ) was independent variable witch influents FMD values. After adjustment for other factors, SLE activity was associated with 1,27% lower FMD compared with control subjects (Table IV).

**Discussions**

Systemic lupus erythematosus is associated with an increased risk of coronary heart disease. The rate ratio for myocardial infarction in women with SLE 35 to 44 years of age was found to be 52 times that of a comparative population [3]. The increased risk of atherosclerosis is not exclusively related to traditional risk factors alone [9]. In the last years, SLE itself appeared like an independent risk factor for atherosclerosis, acting through autoimmune vascular injury [7].

Endothelial dysfunction is represent a widespread phenomenon that occurs at an early stage in the atherogenic process. Because endothelial dysfunction may represent an early stage in atherogenesis, it is important to understand

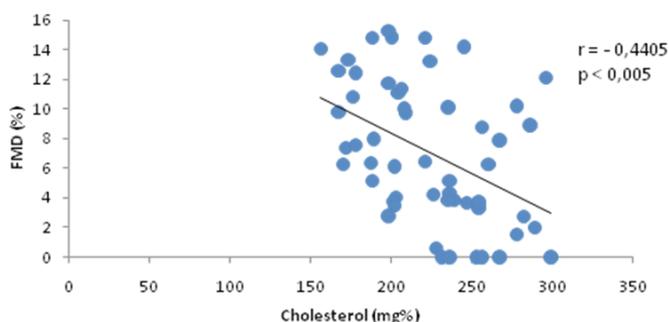


Fig. 2. Correlation between FMD and Cholesterol

**Table IV. Multivariate Analysis in 54 SLE Patients**

	B*	95% CI	p
Age (year)	-.069	-.205–.068	.315
SLE period (year)	-.310	-.540 – -.080	.009
Menopausal state	-.036	-.095 – .023	.227
SBP	-.026	-.081 – .029	.350
DBP	.085	-.017 – .187	.099
DM	-.171	-2.709 – 2.367	.893
Cholesterol (mg%)	-.001	-.018 – .015	.865
HDL-C (mg%)	.391	.030 – .751	.034
TG(mg%)	.007	-.009 – .023	.398
SLEDAI	-1.278	-1.265 – -.891	.000

Multiple coefficient of determination of this model (R<sup>2</sup>) = 0.896.

\* Unstandardized regression coefficient

the mechanisms of its development in a condition such as SLE. It is also important to determine whether it is associated with other CHD risk factors or early atheroma. Therefore, our aims were to determine whether endothelial dysfunction occurred in women with SLE, whether it was explained by the presence of classic CHD risk factors, and whether the SLE activity influence endothelial dysfunction. Lima *et al.* [10], showed that SLE patients presented lower FMD than sex and age-matched controls, even in subjects without traditional cardiovascular risk factors [10]. We chose not to exclude patients with known risk factors to examine the full range of association with FMD in SLE. In our study, FMD in SLE patients was significantly lower than in control subjects ( $p < 0.0001$ ). Piper and Turner in their studies were found that patients with SLE have impaired endothelial function, too [12].

We found a inverse correlation between FMD and SLE-DAI ( $r = -0.5224$ ,  $p < 0.0001$ ) and after adjustment for other factors, SLE activity was associated with 1,27% lower FMD compared with control subjects. Inflammation itself may be associated with endothelial dysfunction. This has been suggested by studies of endotoxin-induced experimental inflammation and in patients with primary systemic vasculitis [13,14]. Therefore, it would be reasonable to expect that inflammatory disease activity in SLE should impair endothelial function, but this was not found in the study by Lima *et al.* [10] were included patients mainly with low disease activity. A prospective study of patients in a clinical flare before and after therapy is therefore warranted to study the influence of SLE inflammation on endothelial function. It is still an attractive hypothesis that chronic inflammation is the key factor contributing to atherosclerosis risk in SLE, yet other mechanisms mediating endothelial dysfunction—eg, insulin

resistance, hyperhomocysteinemia, or ADMA (asymmetric dimethylarginine), a recently described inhibitor of nitric oxide synthase — could be more important in SLE [15]. These require further investigation in the context of SLE.

## Conclusions

In conclusion, we have found impaired endothelial function in SLE that is not fully explained by classic CHD risk factors. Interventions to improve endothelial function in SLE may therefore have an impact on the risk of future CHD. A better understanding of the factors underlying endothelial dysfunction that may specific to SLE is also required to develop novel approaches to reducing the CHD burden in these patients

## References

- Ahmad, Y, Shelmerdine J, Bodill H, *et al.* – Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology*. 2007; 46(6). 983–988
- Urowitz, MB, Bookman AA, Koehler BE, *et al.* – The bimodal mortality pattern of systemic lupus erythematosus. *Am. J. Med.*, 1976, 60, 221–225
- Manzi S, Meilahn EN, Rairie JE *et al.* – Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408–15
- Bruce IN, Burns RJ, Gladman DD, Urowitz MB – Single photon emission computed tomography dual isotope myocardial perfusion imaging in women with systemic lupus erythematosus. I. Prevalence and distribution of abnormalities. *J Rheumatol* 2000;27:2372–7
- El Magadmi M, Bodill H, Ahmad Y *et al.* – Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. *Circulation* 2004;110:399–404
- Esdaille JM, Abrahamowicz M, Grodzicky T *et al.* – Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331–7
- Roman MJ, Shanker BA, Davis A *et al.* – Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Eng J Med* 2003;349:2399–406
- Pearson, JD – Normal endothelial cell function, *Lupus*, 2000, 9, 183–188
- Johnson, SR, Harvey PJ, Floras JS, *et al.* – Impaired brachial artery endothelium dependent flow mediated dilation in systemic lupus erythematosus: preliminary observations, *Lupus*, 2004, 13, 590–593
- Lima DS, Sato EI, Lima VC, *et al.* – Brachial endothelial function is impaired in patients with systemic lupus erythematosus, *Rheumatol J*, 2002, 29(2), 292–297
- Corretti MC, Anderson TJ, Benjamin EJ, *et al.* – Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation at the brachial artery, *J. Am.Coll. Cardiol.*, 2002, 39, 257–265
- Piper MK, Raza K, Nuttall SL, *et al.* – Impaired endothelial function in systemic lupus erythematosus, *Lupus*, 2007, 16(2), 84–88
- Filer AD, Gardner-Medwin JM, Thambyrajah J, *et al.* – Diffuse endothelial dysfunction is common to ANCA associated systemic vasculitis and polyarteritis nodosa. *Ann Rheum Dis*. 2003; 62:162–167
- Hingorani AD, Cross J, Kharbanda RK, *et al.* – Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation*. 2000;102:994–999
- Cooke JP – Does ADMA cause endothelial dysfunction? *ArteriosclernThromb Vasc Biol*. 2000; 20:2032–2037